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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,996	05/24/2000	Mark T. Keating	408-916010US	4041

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 05/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/554,996	Applicant(s) KEATING ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *5,15-21,25 and 40-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-14,22-24 and 26-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that claims 1 and 22 should also be linking claims for group II, and claims 36-38 should be linking claims for groups I and IV.

In view of applicants' argument set forth in the "amendment and response to restriction requirement" filed 3-8-02, claims 36-38 are considered linking claims to groups I and IV with the understanding that claims 36-38 in group I are directed to a method for prophylaxis or treatment of a disorder of diminished regular smooth muscle cell function by using tubular elastin-based composition, wherein the word "tubular" refers to the shape of the elastin-based composition, not its make-up, i.e. not elastin fiber. As requested by applicants, groups I, II and IV are modified as follows:

Group I: Claims 1-4, 6-14, 22-24 and 26-39

Group II: Claims 1, 5, 22 and 25

Group IV: Claims 1, 22 and 36-38

2. Claims 5, 15-21, 25 and 40-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Applicants' amendment filed 3-8-02 has been entered. Claim 22 has been amended. Claims 1-47 are pending. Claims 1-4, 6-14, 22-24 and 26-39 are under consideration.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See M.E.P.. §§ 602.01 and 602.02.

The oath or declaration is defective because:

Applicants claim priority of US Application No. 09/258,217 filed 2-26-99 under 35 U.S.C. 119(e) and 35 U.S.C. 120. US Application No. 09/258,217 is **not** a provisional application, therefore, its priority can not claimed under 35 U.S.C. 119(e). Appropriate correction is required.

Claim Rejections - 35 USC § 112

4.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 3 recites the limitation "said EC50/IC50" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 2 recites IC50/EC/50 not EC50/IC50.

6. Claims 22-24 and 26-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "characterized by" in claim 22 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "characterized by". The specification fails to specifically define the phrase "characterized by". Changing the phrase "characterized by" to "having" would be remedial. Claims 23, 24 and 26-38 depend on claim 22 but fail to clarify the indefiniteness.

The phrase "a method comprising implanting...at a targeted site is selected from the group..." in claim 39 is vague and renders the claim indefinite. It is unclear whether it is the "method" that is selected from the group or "a target site"that is selected from the group. If it is the "method" that is selected from the group, then it is unclear how a method can be selected from the group consisting of various ducts.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 3, 23 and 36-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 3 is directed to the composition of claim 2 wherein the EC50/IC50 is greater than or approximately equal to 10^{-15} M. The phrase "the EC50/IC50 is greater than or approximately equal to 10^{-15} M" is considered a new mater. The specification only discloses IC50/EC50 that is greater than about 10^{-15} M (page 21, lines 14-20) but fails to provide sufficient description and support for **EC50/IC50** that is greater than about 10^{-15} M or **approximately about 10^{-15} M**.

Claim 23 is directed to the method of claim 22 wherein the EC50 is less than or approximately equal to that of SEQ ID No. 2 and is greater than about 1 nM. The phrase "the EC50 is less than or approximately equal to that of SEQ ID No. 2 and is greater than about 1 nM" is considered a new matter. The specification only discloses **IC50/EC50** that is greater than about 10^{-15} M or can be 10^{-9} M, i.e. 1 nM (page 21, lines 14-20) but fails to provide sufficient description and support for **EC50** that is less than or approximately equal to that of SEQ ID No. 2 and is greater than about 1 nM.

The phrase "artificial blood vessel" in claims 36-38 is considered new matter because the specification fails to provide sufficient description and support for the phrase "artificial blood vessel". It is unclear what constitutes an "artificial blood vessel".

9. Claims 1-4, 6-14, 22-24 and 26-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a tropoelastin or 7 repeats of the sequence of SEQ ID No. 1 (VGVAPG) or a method for preventing vascular

restenosis by using said composition *in vitro* or via direct administration of said composition to a targeted site *in vivo*, does not reasonably provide enablement for a pharmaceutical composition comprising any fragment of elastin or tropoelastin and a method for prophylaxis or treatment of a disorder having diminished capacity to regulate smooth muscle cell function by delivering said pharmaceutical composition to a targeted site via any administration route *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-4, 6-14, 22-24 and 25-39 are directed to a pharmaceutical composition that provides an elastin-based composition comprising elastins, tropoelastins, or fragments thereof, to a target site *in vivo*, wherein said composition has one or more biological activities of inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells *in vivo,* and a method for prophylaxis or treatment of a disorder having diminished capacity to regulate smooth muscle cell function by delivering said pharmaceutical composition to a targeted site *in vivo*. Claims 6 and 26 specify said elastin-based composition comprises a recombinant tropoelastin. Claims 7-9 and 27 specify said elastin-based composition comprises a synthetic elastin peptide, such as two repeats or 6 repeats of VGVAPG. Claims 11 and 29 specify the composition comprises an elastin matrix produced from a blood vessel. Claims 12-14, 30 and 31 specify the composition is attached to a biocompatible support. Claim 33 specifies the delivery comprises intravascular delivery directly to a vascular site. Claim 34 specifies the disorder is atherosclerosis, restenosis, aneurysm, vascular bypass graft stenosis, dissection, or transplant

arteropathy. Claims 36-38 specify the pharmaceutical composition is a tubular elastin-based composition as an artificial blood vessel for vascular bypass or coronary artery bypass grafting.

The claims read on using any fragment of various elastins or tropoelastins derived from numerous organisms in a pharmaceutical composition for prophylaxis or treatment of disorder having diminished capacity to regulate smooth muscle cell function. The specification discloses use of a human tropoelastin or 7 repeats of the sequence of SEQ ID No. 1 (VGVAPG) for preventing vascular restenosis *in vitro*. The claims encompass using any fragment of various elastins or tropoelastins derived from numerous organisms to prevent or treat disorders having diminished capacity to regulate smooth muscle cell function. A fragment of a tropoelastin or elastin can range from a few amino acids to several hundreds of amino acids and can have dramatically different amino acid sequences from each other.

The specification fails to provide adequate guidance and evidence that any fragment of a elastin or tropoelastin would have biological activities, such as inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells *in vivo*. The specification also fails to provide information concerning structural feature except the disclosed 7 repeats of VGVAPG that contributes to the function of elastin or tropoelastin for preventing or treating disorders as set forth above. Although 7 repeats of VGVAPG has a function of preventing vascular restenosis, there is no evidence of record that indicates one or two repeats of VGVAPG or other number or VAVGPG repeats alone would have the same biological function as 7 repeats of VAVGPG *in vivo*. Raju et al., 1987 (J. Biol. Chem., Vol. 262(12): 5755-5762)

reports that pentapeptide PGVGV repeat sequence is associated with a labile beta-spiral structure (beta-turn repeat), and "This pentapeptide repeat occurs 11 times between residues 334 and 390...in bovine elastin and also in the corresponding sequence of pig elastin. However, in the corresponding sequence of chicken elastin, this pentapeptide repeat occurs only twice and is followed by a tripeptide repeat (PVG, 12 times; see Fig. 3), This would suggest that the labile beta-labile structure involving this pentapeptide repeat is not essential for the function of elastin" (e.g. p. 5761, right column). Different elastin or tropoelastin derived from different organisms can have different types of repeat that might contribute to the biological function of elastin or tropoelastin. It is unclear whether the VGVAPG repeat and how many VGVAPG repeat is the structural feature required for elastin or tropoelastin having the biological activities as set forth above. Thus, one skilled in the art at the time of the invention would not known whether any fragment of a elastin or tropoelastin, either occurs naturally or synthesized artificially, except the disclosed 7 repeats of VGVAPG would have biological activities, such as inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells, so as to prevent or treat various disorders, such as atherosclerosis, restenosis, aneurysm, vascular bypass graft stenosis, dissection, or transplant arteropathy *in vivo*.

In addition, it was well known in the art that amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure

from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of broad scope of various fragments of elastins or tropoelastins, the lack of detailed information regarding the structural and functional requirements for various elastins or tropoelastins having the biological activities as set forth above, and the unpredictability of polypeptide function from mere amino acid sequence, it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

The phrase "pharmaceutical composition" implies therapeutic effects *in vivo*. The claims read on using the pharmaceutical composition to prevent or treat disorders as set forth above via various administration routes *in vivo*. It was known in the art that administration route of a pharmaceutical composition plays an important role in the efficiency of said composition *in vivo*. The type of administration route determines how the composition comprising elastins or tropoelastins or fragments thereof reach its targeted site *in vivo*. The location of administration, the amount and stability of the polypeptides or peptides *in vivo*, and its compartmentalization within the cell are all important factors in determining whether sufficient polypeptides or peptides can reach their target site so as to provide therapeutic effects for preventing or treating disorders as set forth above *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

11. Claims 1, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Ito et al., 1997 (Cardiovascular Surgery, Vol. 5, No. 2, p. 176-183; IDS-DG).

Claims 1, 10 and 12 are directed to a pharmaceutical composition that provides an elastin-based composition comprising elastins, tropoelastins, or fragments thereof, to a target site *in vivo*, wherein said composition has one or more biological activities of inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells *in vivo*. Claim 10 specifies the composition is crosslinked, precipitated, or coacervated. Claim 12 specifies the composition is attached to a biocompatible support.

Ito teaches preparation of a collagen gel containing alpha-elastin protein at a concentration of 1, 5, and 10 mg/ml. Ito reports that alpha-elastin inhibits the proliferation and migration of smooth muscle cell in a dose-dependent manner on collagen gel culture. It should be noted that the term "pharmaceutical" in a composition claim does not carry weight in a rejection under 35 U.S.C. 102. Collagen is a biocompatible material which supports alpha-elastin. The alpha-elastin protein in collagen gel is crosslinked, precipitated, or coacervated. Thus, claims 1, 10 and 12 are anticipated by Ito.

12. Claims 1 and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Rothstein et al., US Patent No. 5,969,106.

Claims 1 and 6-9 are directed to a pharmaceutical composition that provides an elastin-based composition comprising elastins, tropoelastins, or fragments thereof, to a target site *in vivo*, wherein said composition has one or more biological activities of inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells *in vivo*. Claim 6 specifies said elastin-based composition comprises a recombinant tropoelastin. Claims 7-9 specify said elastin-based composition comprises a synthetic elastin peptide, such as at least two repeats or 6 repeats of VGVAPG (SEQ ID No. 1).

Rothstein teaches a human elastin sequence (SEQ ID No. 1 of the patent) which contains an amino acid sequence of residues 451 to 492 that is 100% identical to SEQ ID No. 2, which contains 7 repeats of VGVAPG, of the present application. Rothstein also teaches production of a recombinant protein containing minimal functional unit (MEU) of human elastin that comprises seven-fold repeats of PGVGVA sequence, and said recombinant protein is contained in fraction 1 in a 0.05M acetic acid solution (e.g. column 12, 13). The recombinant protein containing MEU of human elastin will inherently contain the biological activity of the human elastin, such as inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells. Thus, claims 1 and 6-9 are anticipated by Rothstein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.